REMARKS

The Official Action dated April 10, 2002 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 1, 6-8, 11, 17, 18, 22 and 23 have been amended for various matters of form and clarity, care having been exercised to avoid any introduction of new matter. A Version With Markings Showing Changes Made is attached. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, the Examiner indicated that the specification required an Abstract on a separate sheet. Included herewith is an Abstract on a separate sheet which describes the methods, devices and test kits defined by the present claims. It is therefore submitted that the Examiner's request has been fulfilled.

Claims 1-33 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner objected to various informalities and terminology in the claims.

This rejection is traversed with respect to the present claims. Applicants submit that claims 1-4 and 6-33 particularly point out and distinctly claim the subject matter which Applicants regard as the invention in accordance with the requirements of 35 U.S.C. §112, second paragraph. Reconsideration is respectfully requested.

The Examiner questioned the meaning of various terms including Reactant*, Reactant I, Reactant', the reactants, firmly anchored, n' and n", LZ_n, LZ_{n+1} and the arrow employed in claim 1. Applicants submit that each of these terms is sufficiently defined in the specification as to render the present claims definite to one of ordinary skill in the art.

More particularly, the present application defines biospecific affinity reactants beginning at page 1, line 29. Both the specification and independent claims 1 and 18 define Reactant* as a biospecific affinity reactant which is analytically detectable and define Reactant I as a biospecific affinity reactant which is firmly anchored in the matrix. Reactant' is defined in claim 14 as Reactant I, i.e., the biospecific affinity reactant which is firmly anchored in the matrix, or a reactant to which Reactant I exhibits biospecific affinity and which is transported from the sample liquid application zone (LZ_n'S) or from an application zone downstream of LZ_n'S. This is explained in detail in the specification at page 10, lines 3-10. Additionally, claims 1 and 18 clearly recite that the application zone for liquid (LZ) containing buffer and sample and optionally reactants refers to reactants needed for a complete determination, i.e., of an analyte in a sample in a flow matrix, but not Reactant I, i.e., the biospecific affinity reactant firmly anchored in the flow matrix. Thus, Reactant*, Reactant I, Reactant', and reactants needed for a complete determination, are definite to one of ordinary skill in the art.

With respect to the term "firmly anchored," attention is directed to the specification at page 12, lines 12-14 in which firmly anchored is defined as bonds not allowing unintentional transport of Reactant I under test conditions. As further set forth, "firmly anchored" may encompass attachment of Reactant I to the matrix by covalent bond, via physical absorption, via biospecific affinity, or the like. Additionally, anchoring may be achieved via particles having been deposited in or on the matrix and to which Reactant I is covalently, physically absorptively or biospecifically or the like bound, as described in the paragraph bridging pages 12 and 13. Thus, "firmly anchored" is definite to one of ordinary skill in the art.

The Examiner also objected to the term "substantially" in the recitation that the flow matrix comprises at least two application zones for liquid arranged "substantially adjacent to each other." Attention is directed to the specification at page 6, lines 4-8 which define the

expression "substantially adjacent to each other" as meaning that the application zones for liquid are immediately adjacent to each other or with an intermediate of matrix which preferably is no more than about 2 mm, and particularly no more than about 1 mm. Thus, the expression "substantially adjacent to each other" is definite to one of ordinary skill in the art.

Both claims 1 and 18 have been amended to clarify that the arrow set forth therein references the flow direction with respect to the arrangement of the liquid application zones (LZ) and the detection zone (DZ). These claims define "n" as the position of the application zone LZ_n. When n=1, LZ_n is LZ_1, the first liquid application zone upstream of DZ. Claims 1 and 18 therefore clearly and definitely recite that LZ_m is upstream of LZ_n which, if $n > 1$, is upstream of LZ_1 which is upstream of DZ.

With respect to the subscripts n, n', n", n+1 and m, these subscripts refer to the position of the particular liquid application zone (LZ), as explained in the specification at page 4, line 23 - page 6, line 2. From the specification and claims 1 and 18, it is evident that, of the liquid application zones which are recited, LZ_1 is the closest upstream liquid application zone from the detection zone (DZ), while LZ_m is the farthest upstream liquid application zone. The expression $n" \geq n'$ therefore clearly means that the position of the application zone with the n" subscript is at the same or an upstream position from the DZ as compared to the application zone indicated by subscript n'. Additionally, it is therefore clear to one of ordinary skill in the art that while LZ_n may be LZ_1, wherein $n = 1$, LZ_n is not the same as LZ_{n+1}. As further set forth at pages 4-6 of the specification and as clearly set forth in claims 1 and 18, $LZ_{n'}S$ designates the liquid application zone for sample, while $LZ_{n"}R^*$ designates the application zone for Reactant'.

Finally, from the orientation of the liquid application zones and the detection zone in the flow matrix as defined in the specification and claims 1 and 18, one of ordinary skill in the art will appreciate that the expression ". . ." in the disclosure of the flow matrix zones is

used only to show the relative positions of the respective zones to one another in the flow matrix.

It is believed that the remaining terms objected to the by Examiner have been corrected in the claims and that claims 1-4 and 6-33 are definite in accordance with the requirements on 35 U.S.C. §112, second paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-14, 18-28, 32 and 33 were rejected under 35 U.S.C. §102(b) as being anticipated by the Dafforn et al U.S. Patent No. 4,981,786. The Examiner asserted that Dafforn et al disclose an immunoassay device and method employing a first means for introducing a sample into the device and a second means for introducing a liquid reagent other than the sample into the device upstream of the sample, with both application zones located upstream of an immunosorbing detection zone. The Examiner further asserted that Dafforn et al disclose specific binding members immobilized in the immunosorbing zone and that the application of liquid can be performed simultaneously in the application zones.

However, Applicants submit that the methods, devices and test kits defined by claims 1-4, 6-14, 18-28, 32 and 33 are not anticipated by and are patentably distinguishable from Dafforn et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as defined by claims 1 and 18, the present invention is directed to methods and devices for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I). The flow matrix comprises an application zone for liquid (LZ) containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I, a detection zone with Reactant I located downstream of LZ, and optionally one or more zones

in which any of the reactants has been pre-deposited. The flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other :

$LZ_m \ldots LZ_n \ldots LZ_l$ DZ

flow direction

wherein LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n, m is the total number of application zones in which flow is initiated ($m \geq 2$), one LZ_n is an application zone for sample (LZ_n,S) and one LZ_n is for Reactant* (LZ_n,R*), with n" $\geq$ n', ⟶ is the direction of the flow, and DZ is the detection zone. Flow is initiated by adding liquid to each zone LZ_m . . LZ_n . . LZ_l ($m \neq n$) in such a way that $liquid_{n+1}$, added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after $liquid_n$ added to the nearest downstream application zone LZ_n. The present methods and devices facilitate automation of analyte determination, avoid the need for sequential addition of sample and analytically detectable reactant, and allow for predeposited analytical reactant for sequential methodologies.

Dafforn et al disclose a multiple port assay device. Delivery of a sample may be made into the device through a first means or second means using a dropper, syringe needle, etc., resulting in deposit of the sample on a bibulous strip, and a liquid reagent other than sample is added to the device following addition of the sample. Additional liquid reagents may be added to the device either before or after sample addition, at least one of such reagents being added through the means not used for adding the sample (column 13, lines 32-42). The application of reagents can also be done by breaking the container (column 23, line 52). Dafforn et al specifically provide that liquid may be transported by capillary action away from a zone where a first member of a specific binding pair is captured (column 3, lines 4-8).

However, Applicants find no teaching or suggestion by Dafforn et al relating to a method or device as presently claimed wherein at least one biospecific affinity reactant (Reactant I) is firmly anchored in the flow matrix and at least one biospecific affinity reactant is applied to an application zone in combination with a flow matrix arrangement as recited in claims 1 and 18. Particularly, Applicants find no teaching or suggestion by Dafforn et al of a method or device wherein flow is initiated by adding liquid to each zone in such a way that $liquid_{n+1}$ added to the application LZ_{n+1} contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after $liquid_n$, added to the nearest downstream application zone LZ_n. In fact, while Dafforn et al disclose sequential addition of sample and reagent, Applicants find no other teaching or suggestion by Dafforn et al relating to a flow matrix as presently claimed, or the flow of different liquid application zone liquids therein as presently claimed.

Thus, in the present methods and devices, sample and reagent may be applied to the flow matrix almost simultaneously. The sample begins migration to the detection zone and is followed by liquid migration from the next upstream zone. As a result, there is a continuous migration of sample and reagents through the flow matrix, started by one initial application occasion. The flow of liquids through the flow matrix and the detection zone is created in the same order as they are added in the application zone. Applicants find no such teachings by Dafforn et al.

Anticipation under 35 U.S.C. §102 requires that each and every element set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q.2d 1949, 1950 (Fed Cir. 1999). In view of the deficiencies in the teachings of Dafforn et al, Dafforn et al do not anticipate the present claims under 35 U.S.C. §102. It is therefore submitted that the rejection under 35 U.S.C. §102 based on Dafforn et al has been overcome. Reconsideration is respectfully requested.

Claims 15, 16, 29 and 30 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Robinson et al published PCT application WO 95/16914. The Examiner relied on Robinson et al as disclosing the use of calibration zones. The Examiner asserted it would have been obvious to incorporate the use of a calibrator zone as taught by Robinson et al in the method and device of Dafforn et al.

However, Applicants submit that the methods and devices defined by claims 15, 16, 29 and 30 are nonobvious over and patentably distinguishable from the combination of Dafforn et al in view of Robinson et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, the deficiencies of Dafforn et al are discussed in detail above. These deficiencies are not resolved by Robinson et al. Robinson et al describe a sensor device for a sandwich assay comprising a discrete zone having a measurement region on which is immobilized a first specific binding partner for a ligand under assay and a known amount of a releasable optionally labeled second specific binding partner for the ligand under assay, and a second discrete zone having a region on which is immobilized a first specific binding partner for the ligand under assay, a releasable known amount of ligand analog, and a second known amount of a second optionally labeled second specific binding partner for the ligand under assay.

However, Applicants find no teaching or suggestion for employing any of the elements of Robinson et al's sensor device in the multiple port assay device of Dafforn et al. In fact, while Dafforn et al require application of one or more liquid reagents in addition to a liquid sample through different introduction means, the sensor device of Robinson et al is designed for a sandwich assay wherein only a sample containing a ligand under assay is applied. Only in hindsight of the methods and devices recited in claims 15, 16, 29 and 30

would one of ordinary skill in the art have any motivation for combining the teachings of Dafforn et al and Robinson et al along the lines of the present invention.

Moreover, Applicants find no teaching or suggestion by Robinson et al for resolving the deficiencies of Dafforn et al. That is, Applicants find no teaching or suggestion by Robinson et al of a method or device as recited in claims 1 and 18, respectively, employing at least one analytically detectable biospecific affinity reactant (Reactant*) and at least one firmly anchored biospecific affinity reactant (Reactant I) in a detection zone, with the arrangement of liquid application zones and liquid flows as recited in claims 1 and 18.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the failure of Robinson et al to resolve the deficiencies of Dafforn et al, the combination of these references does not enable one of ordinary skill in the art to conduct the claimed method or make and use the claimed device. Thus, the combination of Dafforn et al and Robinson et al does not render claims 15, 16, 29 and 30 obvious. It is therefore submitted that the rejection of these claims under 35 U.S.C. §103(a) has been overcome. Reconsideration is respectfully requested.

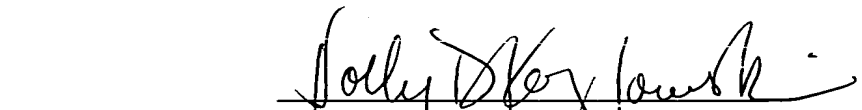
Finally, claims 17 and 31 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Self U.S. Patent No. 4,446,231. The Examiner relied on Self as disclosing that immunoassays are used for the detection and/or determination of autoimmune diseases. The Examiner asserted it would have been obvious to use immunoassays as taught by Self for the diagnosis of autoimmune diseases.

However, Applicants submit that the methods and devices defined by claims 17 and 31 are nonobvious over and patentably distinguishable from the combination of Dafforn et al and Self. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Dafforn et al are discussed in detail above. These deficiencies are not resolved by Self. That is, while Self discloses an immunoassay using an amplified cyclic detection system, Applicants find no teaching or suggestion by Self relating to a method or device for determination of an analyte in a sample and a flow matrix employing a combination of biospecific affinity reactants and liquid application zones and flow as defined in claims 1 and 18. Similarly, Applicants find no teaching or suggestion by Self for modifying any of the teachings of Dafforn et al to result in either a method or a device as presently claimed. Thus, the mere teaching by Self of the use of immunoassays for detection and/or determination of autoimmune diseases does not resolve the deficiencies of Dafforn et al, whereby the combination of Dafforn et al and Self does not render the methods and devices of claims 17 and 31 obvious. It is therefore submitted that the rejection of these claims under 35 U.S.C. §103 based on Dafforn et al and Self has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§ 102, 103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Specification:

The paragraph at page 4, line 23 - page 5, line 2, is amended as follows:

A. the flow matrix exhibits at least two application zones for liquid arranged substantially adjacent to each other:

$LZ_m \ldots LZ_n \ldots LZ_1$ DZ

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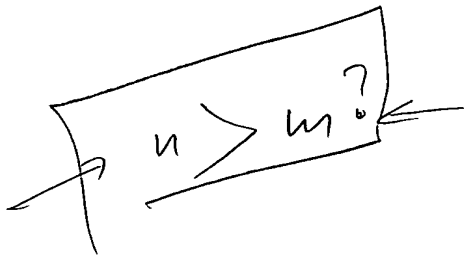


wherein

a) LZ_n is an application zone for liquid, where n is the position of the application zone LZ_n [(n is an integer $2 < n \leq m$)], → New matter

b) m is the total number of application zones, in which the flow is initiated,

c) one LZ_n is an application zone for sample (LZ_n, S) and one LZ_n is application zone for Reactant* ($LZ_{n''}$ R*) with $n'' \geq n'$,

d) ----------> is the direction of the flow, and

e) DZ is detection zone, and

In the Claims:

Claims 1, 6-8, 11, 17, 18, 22 and 23 are amended as follows:

1. (Twice Amended) A method for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I), and the flow matrix comprises:

A) an application zone for liquid (LZ), containing buffer and sample and optionally [one or more of the] reactants needed for a complete determination, but not Reactant I,

B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ [with the firmly anchored reactant (Reactant I)], and

C) optionally one or more zones in which any of the reactants needed for a complete determination, but not Reactant I, has been pre-deposited,

wherein (i) the flow towards the detection zone is initiated by addition of the liquid with sample in the application zone [LZS] LZ for transport of analyte and reactants towards the detection zone (DZ), and (ii) the amount of the Reactant* bound to DZ is detected, wherein the detected amount [being related] is correlated to the amount of analyte in the sample, wherein

I. the flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:

$LZ_m \ldots LZ_n \ldots LZ_l$ DZ

flow direction 

wherein

a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n,

b) m is the total number of application zones in which flow is initiated ($m \geq 2$),

c) one LZ_n is an application zone for sample (LZ_n'S) and one LZ_n is for Reactant* (LZ_n"R*) with $n'' \geq n'$;

d) ⟶ is the direction of the flow, and

e) DZ is the detection zone, and

II. flow is initiated by adding liquid to each zone $LZ_m \ldots LZ_n \ldots LZ_l$ ($m \neq n$) in such a way that $liquid_{n+1}$, added to the application zone LZ_{n+1}, contacts the flow matrix

substantially simultaneously and is transported through the matrix immediately after liquid$_n$[,] added to the nearest downstream application zone LZ_n.

6. (Twice Amended) The method according to claim 1, wherein LZ_{n+1} finishes where LZ_n starts ($m \neq n$) [, with the exception of n=m, which zone lacks the zone LZ_{n+1}].

7. (Twice Amended) The method according to claim 1, wherein application of liquid is performed [substantially] simultaneously in all LZ_m . . LZ_n . . LZ_1.

8. (Twice Amended) The method according to claim 1, wherein $m \leq 6$; n' is 1, 2 or 3, n" > n'; $LZ_{n'+1}$, $LZ_{n'+2}$, $LZ_{n'+3}$, $LZ_{n'-1}$, and $LZ_{n'-2}$ are application zones for liquids intended for transport of Reactant* or other reactant or buffer without reactant[, as far as allowed by m, n" and n'].

11. (Twice Amended) The method according to claim 1, wherein [the] a composition of transported components from an application zone LZ_n is not the same as from the nearest adjacent application zone LZ, in which flow is initiated, (LZ_{n+1} and LZ_{n-1}[, with the exception of n=m and n=1, which zones lack LZ_{n+1} and LZ_{n-1}, respectively).]

17. (Twice Amended) The method according to claim 1, wherein

[a. the analyte is chosen among antigens generally, and

b.] the method is performed as part of diagnosing allergy or autoimmune disease.

18. (Twice Amended) A device for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I), said device comprising a flow matrix having:

A) an application zone for liquid (LZ), containing buffer and sample and optionally [one or more of the] reactants needed for a complete determination, but not Reactant I,

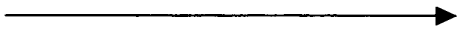
B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ [with the firmly anchored reactant (Reacant I)], and

C) optionally one or more zones in which any of the reactants has been pre-deposited,

wherein

the flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:

$LZ_m \ldots LZ_n \ldots LZ_1$ DZ



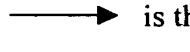
flow direction 

wherein

a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n,

b) m is the total number of application zones in which flow is initiated ($m \geq 2$),

c) one LZ_n is an application zone for sample ($LZ_{n'}S$) and one LZ_n is for Reactant* ($LZ_{n''}R^*$) with $n'' \geq n'$;

d)  is the direction of the flow, and

e) DZ is the detection zone, wherein the device is adapted, when flow is initiated by adding liquid to each zone LZ_m . . LZ_n . . LZ_1 ($m \neq n$) in such a way that $liquid_{n+1}$, added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously to transport the $liquid_{n+1}$ through the matrix immediately after $liquid_n$, added to the nearest downstream application zone LZ_n.

22. (Twice Amended) The device according to claim 18, wherein LZ_{n+1} finishes where LZ_n starts ($m \neq n$) [, with the exception of n=m, which zone lacks the zone LZ_{n+1}].

23. (Twice Amended) The device according to claim 18, wherein $m \leq 6$; n' is 1, 2 or 3; n'' > n; $LZ_{n'+1}$, $LZ_{n'+2}$, $LZ_{n'+3}$, $LZ_{n'-1}$, and $LZ_{n'-2}$ are application zones for liquids intended for transport of Reactant* or other reactant or buffer without reactant[, as far as allowed by m, n'' and n'].